PROC (BAYL UNIV MED CENT)
2021;34(5):555–559

https://doi.org/10.1080/08998280.2021.1930967

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Relation of apixaban bleeding rates to dose in patients with chronic kidney disease

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ABSTRACT

The objective of this study was to evaluate the safety and efficacy of apixaban 5 mg twice daily vs 2.5 mg twice daily for nonvalvular atrial fibrillation or venous thromboembolism in patients with chronic kidney disease stage 4 and 5, including those on hemodialysis. Data were collected retrospectively on patients with advanced chronic kidney disease and nonvalvular atrial fibrillation and/or venous thromboembolism who received apixaban while hospitalized at our institution between January 2013 and August 2018. The 5 mg twice daily group included 22 patients, and the 2.5 mg twice daily group included 73 patients. There was no difference between groups in major bleeding events (9.1% vs. 12.3%, $P = 1.00$), any bleeding event (45.4% vs. 67.1%, $P = 0.08$), ischemic stroke (0% vs. 2.7%, $P = 1.00$), or venous thromboembolism (4.5% vs. 0%, $P = 0.23$). Subgroup analyses of patients with a serum creatinine >2.5 mg/dL or creatinine clearance <25 mL/min and patients on hemodialysis produced similar results. Until larger trials are conducted, clinicians should make patient-specific decisions about the optimal dose of apixaban in patients with severe renal impairment.

KEYWORDS Anticoagulation; apixaban; atrial fibrillation; bleeding; ischemic stroke; renal impairment; venous thromboembolism

Direct oral anticoagulants result in similar or fewer bleeding-related adverse events compared to warfarin without compromising efficacy for nonvalvular atrial fibrillation (NVAF) and for the treatment of venous thromboembolism (VTE).[1–11] However, patients with serum creatinine (SCr) >2.5 mg/dL or a calculated creatinine clearance (CrCl) <25 mL/min were excluded from ARISTOTLE and AMPLIFY, the trials that led to the approval of apixaban for NVAF and VTE.[5,6] Smaller retrospective studies of this population have found that apixaban results in similar if not fewer bleeding-related adverse events when compared to warfarin, but outcomes were not compared between doses of apixaban.[12–14] Based on available evidence and manufacturer recommendations, the optimal dose of apixaban for NVAF and VTE in patients with chronic kidney disease (CKD) stage 4 and 5, including those on hemodialysis (HD), is still unclear. The objective of this study was to evaluate the safety and efficacy of apixaban 2.5 mg twice daily versus 5 mg twice daily for NVAF or VTE in patients with CKD stage 4 and 5, including those on HD.

METHODS

This was a retrospective, single-site cohort study. Patients were identified for inclusion after an index hospitalization at Massachusetts General Hospital (MGH), a tertiary-care academic medical center with over 1000 beds. MGH is part of a health system that comprises two academic medical centers, eight additional hospitals, and several community health centers. Health care entities within the system share a single electronic medical record, and all information throughout the health system for included patients was reviewed.

Patients aged 18 years or older were screened for inclusion if they received at least one dose of apixaban while hospitalized at MGH between January 1, 2013, and August 31, 2018, and had recorded evidence of CKD stage 4 or 5 by *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Edition*

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Supplemental material for this article is available online at https://doi.org/10.1080/08998280.2021.1930967.

The authors report no conflicts of interest.

Received March 31, 2021; Revised May 12, 2021; Accepted May 13, 2021.

(ICD-10). Patients were excluded if they were receiving anticoagulation for an indication other than NVAF or VTE, had a history of an abnormal bleeding or coagulation disorder, had bleeding due to other causes such as trauma, received more than one dose of other oral anticoagulants in the previous 5 days, were nursing or pregnant, were receiving forms of renal replacement therapy other than HD, or if CrCl could not be calculated because baseline weight or SCr was missing.

Patients who met the inclusion criteria were categorized into groups based on the dose of apixaban received on the index date. The index date was defined as the date of the first documented administration of apixaban while hospitalized at MGH within the specified time frame. Information about bleeding and thrombotic events was collected for each patient from the index date until the last date of follow-up available in the electronic medical record. The last date of follow-up was defined as the date apixaban was discontinued, the date of change in apixaban dose, or, if neither event was documented, the date of the last documented note in the patient's medical record. A list of terms for bleeding and thrombotic events was developed and entered into the medical record's search function (Supplementary Material). This study was approved by the Partners Health Care Institutional Review Board.

The primary safety outcome of the study was major bleeding events during the study period. The primary efficacy outcome was ischemic stroke or VTE during the study period. The secondary outcome was a composite of major bleeding events, clinically relevant nonmajor bleeding events, and minor bleeding events during the study period.

The definition of major bleeding from the International Society of Thrombosis and Hemostasis was used to identify major bleeding events.[12] Events were categorized as major bleeding if they were fatal, accompanied by a drop in hemoglobin level of 2 g/dL or more within a 48-hour time frame, or in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome.[11,12] Clinically relevant nonmajor bleeding was defined as clinically overt bleeding that did not satisfy criteria for major bleeding but led to physician-guided medical or surgical treatment, hospitalization, or change in antithrombotic therapy. All other bleeding events were categorized as minor bleeding. Ischemic stroke and VTE events were included if they were documented in the patient's electronic medical record and confirmed with imaging techniques (ventilation/perfusion scan, magnetic resonance imaging, computed tomography, or Doppler ultrasound).

IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY) was used to conduct all analyses. Continuous data were analyzed with the Mann-Whitney U test and presented as means (standard deviation) if normally distributed and medians (interquartile range) if nonnormally distributed.

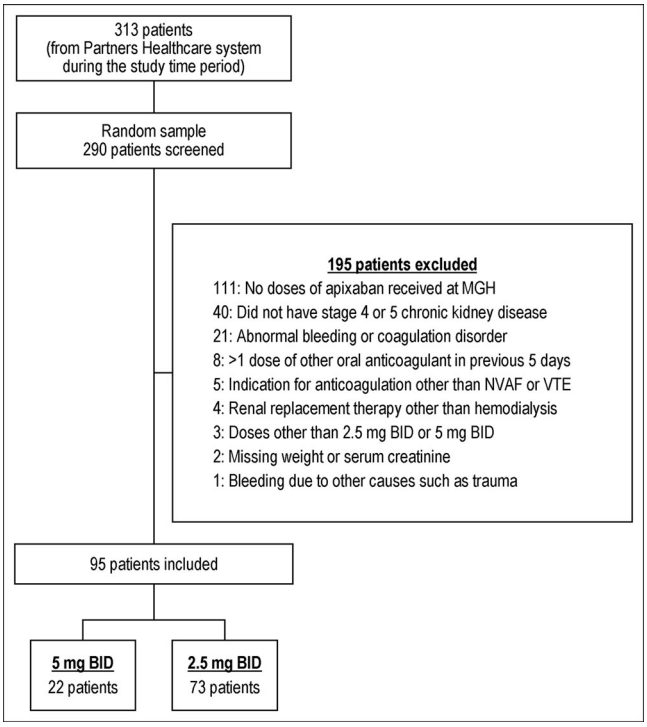

Figure 1. Schematic of patient selection process and reasons for exclusion. BID indicates twice daily; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.

Categorical data were analyzed using the Fisher's exact test and presented as number (percentage).

RESULTS

Upon initiation of the study, 290 patients were screened for inclusion and 98 patients were included. Of the included patients, 22 were receiving 5 mg twice daily, 73 were receiving 2.5 mg twice daily, and 3 were receiving 10 mg twice daily. The most common reason that patients were excluded was because doses of apixaban were received only at other institutions within the health system. Other reasons for exclusion are presented in *Figure 1*.

Baseline demographics and clinical characteristics of included patients are presented in *Table 1*. Patients in the 2.5 mg twice daily group were older ($P = 0.001$), had a lower body mass index ($P = 0.004$), and had lower CrCl ($P = 0.001$) compared to patients in the 5 mg twice daily group. Patients in the 2.5 mg twice daily group also had higher $CHADS_2$ ($P = 0.02$), CHA_2DS_2-VASc ($P = 0.02$), and HAS-BLED ($P = 0.01$) scores. The percentage of patients who had severe renal impairment (SCr >2.5 mg/dL or CrCl <25 mL/min) that would have excluded them from studies such as AMPLIFY and ARISTOTLE was similar in each group. Patients were most commonly receiving apixaban for NVAF (72.7% in the 5 mg twice daily arm and 80.8% in the 2.5 mg twice daily arm), and of the patients with NVAF, 46% were receiving appropriate doses according to the package insert. All NVAF patients not dosed

Table 1. Baseline demographic and clinical characteristics of patients with chronic kidney disease receiving apixaban

Characteristic	5.0 mg BID (n = 22)	2.5 mg BID (n = 73)	*P* value[e]	10 mg BID (n = 3)
Age, median years (IQR)	67 (60–73)	76 (65–86)	0.001	82 (75–83)
Men	13 (59%)	32 (44%)	0.23	2
Weight, median (kg) (IQR)	98.1 (82.5–107.6)	77.4 (67.1–94.5)	0.001	86.5[a]
BMI, median (kg/m^2) (IQR)	35.7 (28.2–39.0)	28.2 (24.1–34.3)	0.004	29.1 (15.4–30.8)
Renal function				
CKD stage 4	11 (50%)	33 (45%)	0.81	2
CKD stage 5	1 (5%)	5 (7%)	1.00	0
Hemodialysis	10 (46%)	35 (48%)	1.00	1
Severe renal impairment[b]	18 (82%)	68 (93%)	0.20	1
SCr, median (mg/dL) (IQR)[c]	2.32 (2.14–2.88)	2.41 (1.99–2.88)	0.94	1.92 (1.82–2.01)
CrCl, median (mL/min) (IQR)[c]	27 (23–33)	20 (15–24)	0.001	29 (29–30)
Indication				
NVAF	16 (73%)	59 (81%)	0.55	0
VTE	4 (18%)	11 (15%)	0.74	2
Both	2 (9%)	3 (4%)	0.33	1
$CHADS_2$ score, median (IQR)[d]	3 (2–3)	3 (3–4)	0.02	4 (4–4)
CHA_2DS_2-VASc score, median (IQR)[d]	4 (4–5)	5 (4–6)	0.02	7 (6–7)
HAS-BLED score, median (IQR)	2 (2–3)	3 (2–4)	0.01	4 (3–5)
Concomitant medications				
Aspirin	8 (36%)	44 (60%)	0.06	1
Proton pump inhibitor	13 (59%)	36 (49%)	0.42	1
Histamine 2 receptor antagonist	1 (5%)	4 (6%)	1.00	0
Nonsteroidal anti-inflammatory	0	0	–	0
P2Y12 inhibitors	1 (5%)	8 (11%)	0.68	0
Strong CYP3A4 inhibitors/inducers	0	0	–	0
Length of follow-up, median (days) (IQR)	121 (10–310)	181 (31–345)	0.51	7 (4–8)

[a]Unable to calculate IQR.
[b]Severe renal impairment: SCr >2.5 mg/dL, CrCl <25 mL/min, or hemodialysis.
[c]Among patients not on hemodialysis.
[d]Among patients with NVAF.
[e]For comparison between 5.0 and 2.5 mg doses.
BID indicates twice daily; BMI, body mass index; CKD, chronic kidney disease; CrCl, creatinine clearance; IQR, interquartile range; NVAF, nonvalvular atrial fibrillation; SCr, serum creatinine; VTE, venous thromboembolism.

according to the package insert were receiving 2.5 mg twice daily. Among the patients receiving apixaban for VTE, 70% of patients were receiving 5 mg twice daily. All patients in the 10 mg twice daily group were receiving apixaban for VTE, one of whom had severe renal impairment.

Results of major and all other bleeding events are presented in *Table 2*. No significant differences between groups were observed. Subgroup analyses were performed on bleeding event outcomes in patients with severe renal impairment not on HD and patients on HD, and no significant differences were observed between dose groups. In the patients who were inappropriately dose reduced according to manufacturer recommendations, 7 patients (14.6%) experienced major bleeding events and 34 patients (70.8%) experienced any bleeding event. None of the patients in the 10 mg twice daily group experienced bleeding events.

Results of thrombotic events are presented in *Table 3*. No significant differences between groups were observed.

Table 2. Proportion of patients with chronic kidney disease receiving apixaban who experienced bleeding events

Population	5 mg BID	2.5 mg BID	*P* value[a]	10 mg BID
Overall	n = 22	n = 73		n = 3
Composite	10 (46%)	49 (67%)	0.08	0
Major	2 (9%)	9 (12%)	1.00	0
CRNMB	5 (23%)	17 (23%)	1.00	0
Minor	8 (36%)	40 (55%)	0.07	0
SCr >2.5 mg/dL or CrCl <25 mL/min	n = 8	n = 33		n = 0
Composite	4 (50%)	22 (67%)	0.43	–
Major	0	5 (15%)	0.56	–
CRNMB	1 (13%)	7 (21%)	1.00	–
Minor	3 (38%)	16 (49%)	0.70	–
Hemodialysis	n = 10	n = 35		n = 1
Composite	4 (40%)	24 (69%)	0.14	0
Major	1 (10%)	4 (11%)	1.00	0
CRNMB	3 (30%)	8 (23%)	0.69	0
Minor	4 (40%)	22 (63%)	0.28	0

[a]For comparison between 5.0 and 2.5 mg BID doses.
BID indicates twice daily; CRNMB, clinically relevant nonmajor bleeding.

Table 3. Proportion of patients with chronic kidney disease receiving apixaban who experienced thrombotic events

Outcome	5 mg BID (n = 22)	2.5 mg BID (n = 73)	*P* value[a]	10 mg BID (n = 3)
Ischemic stroke	0	2 (3%)	1.00	0
Venous thromboembolism	1 (5%)	0	0.23	0

[a]For comparison between 5.0 and 2.5 mg BID doses.

Two patients in the 2.5 mg twice daily arm experienced ischemic strokes, and one patient in the 5 mg twice daily arm experienced a VTE while receiving apixaban. None of the patients in the 10 mg twice daily group experienced ischemic stroke or VTE.

DISCUSSION

Manufacturer recommendations for apixaban dosing in patients with renal impairment are based on data that is not generalizable to patients with more severe renal impairment. Furthermore, studies that have attempted to shed light on optimal dosing for these patients have found conflicting results. Our retrospective cohort study is one of the first to compare outcomes between doses of apixaban in all patients who had SCr >2.5 mg/dL, CrCl <25 mL/min, or HD-dependent renal disease.

For patients on HD, there are studies that provide additional data on apixaban use.[15–17] The original manufacturer recommendation for no additional dose adjustments for HD patients was supported by a study performed by Wang et al.[9,15] This study concluded that a single 5 mg dose of apixaban in eight HD patients increased apixaban exposure by only 36% and did not require dose adjustment.[15] Subsequently, Mavrakanas et al studied seven HD patients with NVAF and found that the area under the curve values at steady state in HD patients who received 5 mg twice daily were above the 90th percentile of what is expected with normal renal function.[16] The authors concluded that 2.5 mg twice daily should be the maximum dose in HD patients. Though this study was performed only in patients with NVAF, a separate study by Steuber et al suggests that the recommendation could be applied to patients with VTE as well.[17] Steuber et al performed a logistic regression of 114 patients on HD who were receiving apixaban for NVAF or VTE and found that increased total daily doses of apixaban were correlated with a higher likelihood of bleeding events. The studies by Mavrakanas et al and Steuber et al suggest that using the 2.5 mg twice daily dose in all HD patients would be associated with improved safety outcomes. In contrast, a retrospective claims-based study of HD patients with NVAF by Siontis et al involved 2351 patients taking apixaban. It found that when compared to warfarin, both the 5 mg twice daily and 2.5 mg twice daily doses of apixaban were associated with lower risks of major bleeding, but only the 5 mg twice daily dose was associated with reduced thromboembolic events and mortality.[4]

Our study found no significant differences between the 2.5 mg twice daily and 5 mg twice daily dose groups with regards to major bleeding, ischemic stroke, VTE, or any bleeding. Our results for percentage of patients who experienced major bleeding events, ischemic strokes, and VTE are generally consistent with those in the previously mentioned retrospective studies comparing apixaban and warfarin in this population with more severe renal impairment. However, a higher percentage of our patients experienced the composite outcome of any bleeding compared to previous studies that evaluated a similar outcome. This may be explained by differences in methods of identifying bleeding events.

In our study, minor bleeding events accounted for a large portion of overall bleeding events. Many of these minor bleeding events were instances of bruising, and while the severity of these events may have varied widely, they were all recorded for purposes of this study because there was not a reliable way to categorize them. The study by Sarrat et al relied largely on paper charts, and Stanton et al relied on a medical record that similarly could not be searched for key words.[12,14] It is possible that our methods allowed for easier identification of minor bleeding events and resulted in a higher percentage of patients who experienced a bleeding

event. It is also worth noting that while there was not a statistically significant difference between groups with regards to the length of follow-up, the 2.5 mg twice daily group had a longer median follow-up time (181 days vs. 121 days), allowing for the identification of more bleeding and thrombotic events.

Several limitations exist in this study. The small sample size and the ending of follow-up when a patient switched doses of apixaban may have limited the ability to detect a significant difference in outcomes. Additionally, initiation of dialysis during the follow-up period was captured, but other changes in renal function, such as progression from stage 4 to stage 5 CKD or improvement in renal function between the index date and the end of follow-up, were not. There are also other components that could have been missed due to the retrospective nature of this study. Patients who were admitted to the study institution for a bleeding or thrombotic event while on apixaban but had apixaban held upon admission as well as those who experienced events at institutions outside of the health system would not have been captured. Those who experienced bleeding events may have had their apixaban doses reduced, and this could have biased our 2.5 mg twice daily dose group toward a higher propensity for bleeding.

In conclusion, the appropriate dose of apixaban for NVAF and VTE in patients with CKD stage 4 and 5, including those on HD, is still unclear. This study is one of the first to evaluate outcomes with apixaban in all patients with SCr >2.5 mg/dL or CrCl <25 mL/min. We found no significant difference between the 2.5 mg twice daily and 5 mg twice daily dose groups with regards to major bleeding, ischemic stroke, VTE, or any bleeding. Larger patient populations should be evaluated in randomized trials to determine the optimal dose. Until more definitive data exist, clinicians should continue to make patient-specific decisions to select a dose of apixaban in patients with severe renal impairment.

ACKNOWLEDGMENTS

The authors thank Douglas Hayden, PhD, for assistance with statistical analysis.

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